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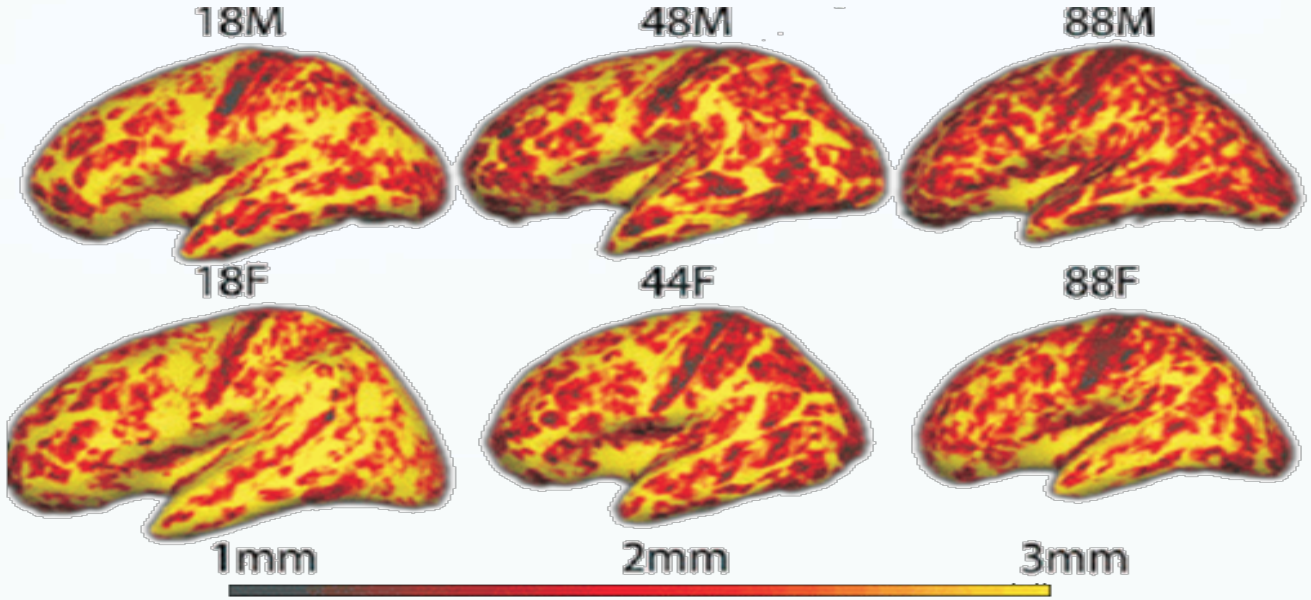
Surface-based Group Analysis in FreeSurfer

Outline

- Processing Stages
- Command-line Stream
  - Assemble Data
  - Design/Contrast (GLM Theory)
  - Analyze
  - Visualize
- Interactive/Automated GUI (QDEC)
- Correction for multiple comparisons

Aging Exploratory Analysis

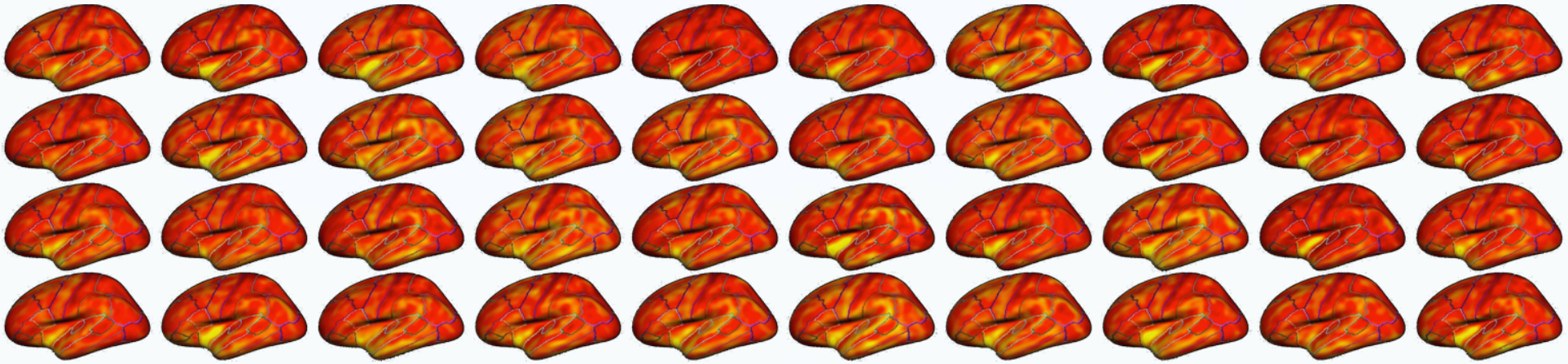


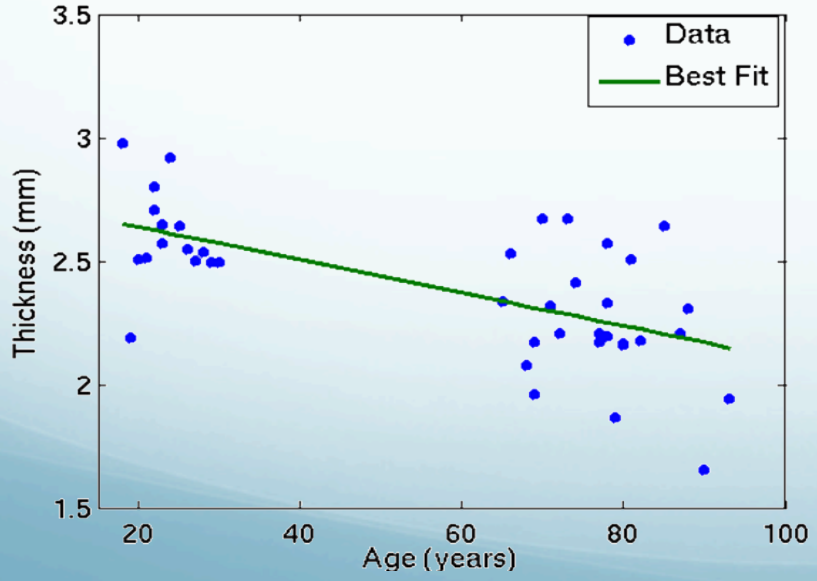
In which areas does thickness
Change with age?

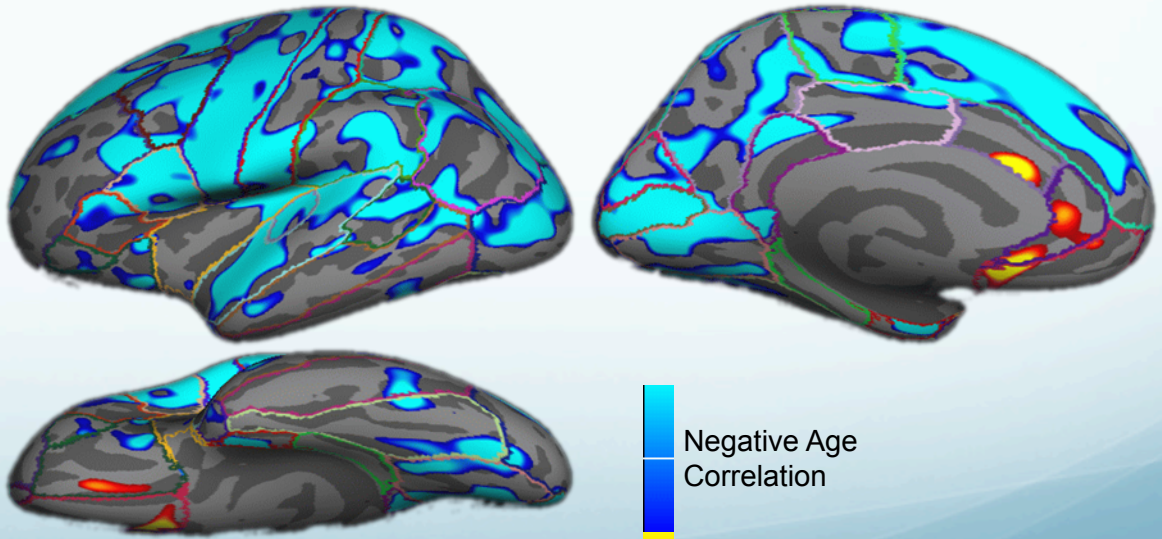
Cortical Thickness vs Aging
Salat et al, 2004, Cerebral Cortex

Aging Thickness Study

N=40 (all in fsaverage space)







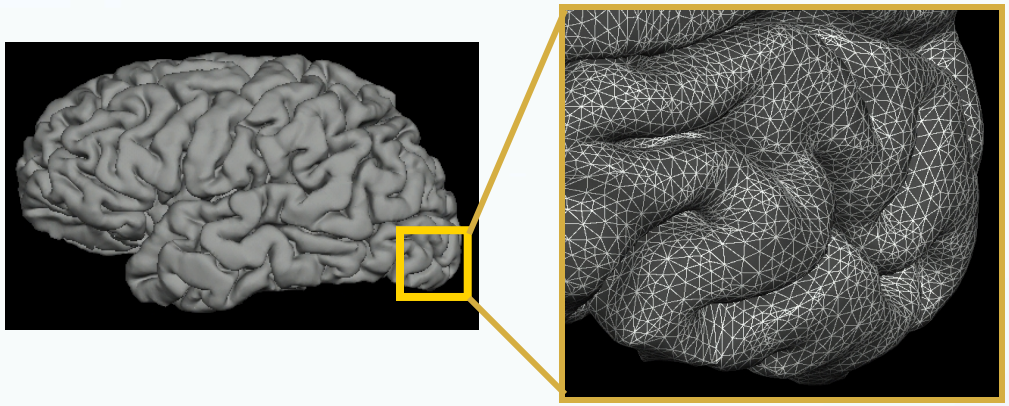
p<.01

Negative Age Correlation

Positive Age Correlation

Surface-based Measures

- Morphometric (e.g., thickness)
- Functional
- PET
- MEG/EEG
- Diffusion (?) sampled just under the surface



Processing Stages

- Specify Subjects and Surface measures
- Assemble Data:
  - Resample into Common Space
  - Smooth
  - Concatenate into one file
- Model and Contrasts (GLM)
- Fit Model (Estimate)
- Correct for multiple comparisons
- Visualize

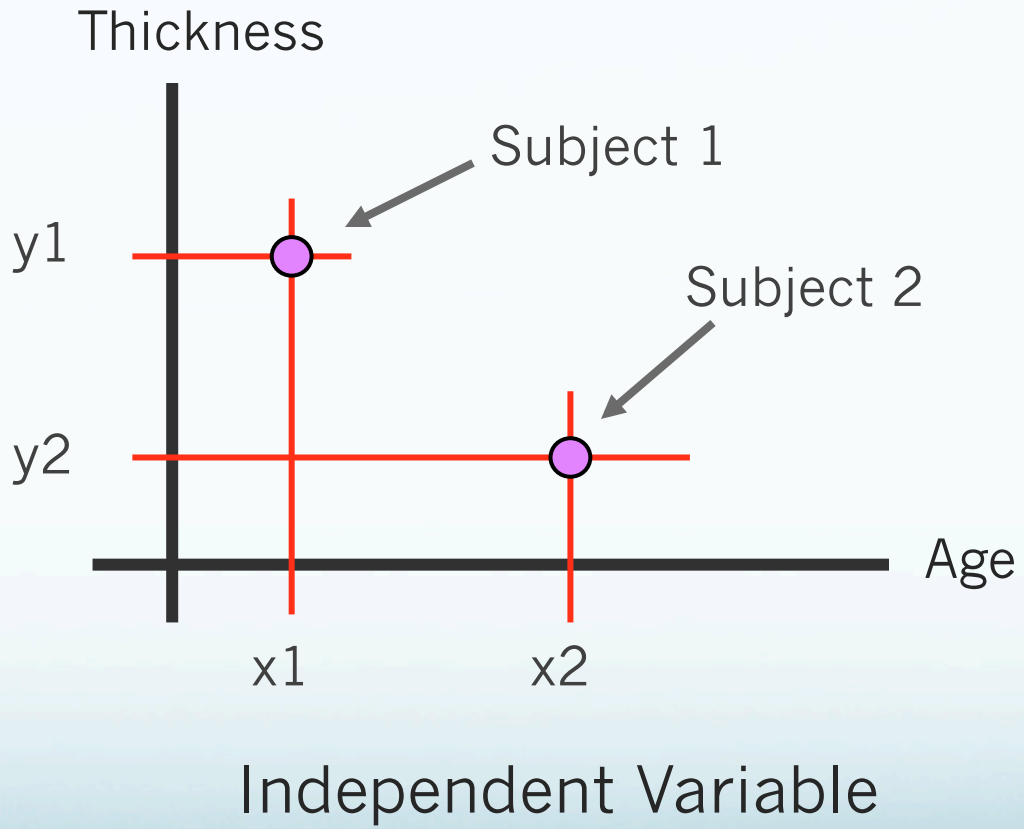
The General Linear Model (GLM)

GLM Theory

Is Thickness correlated with Age?

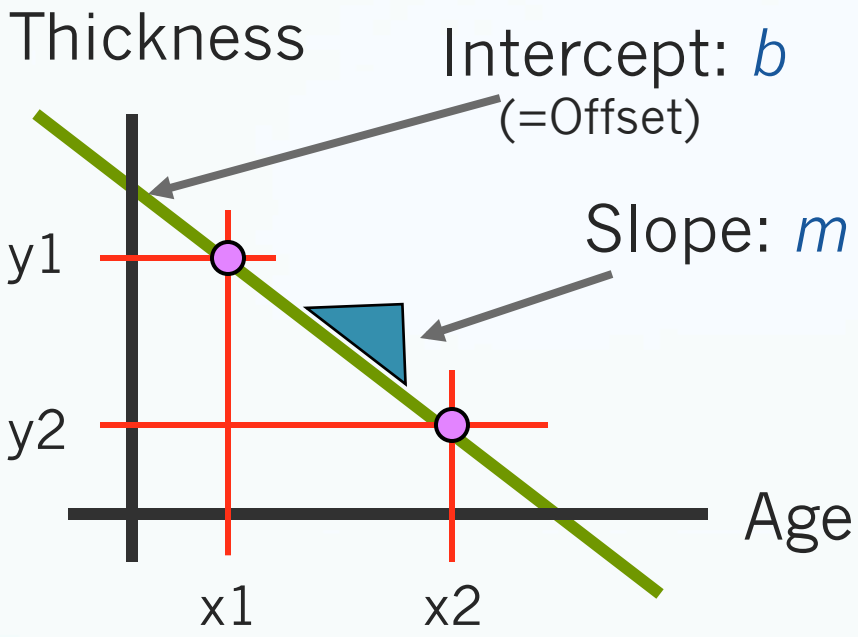
Dependent Variable, Measurement

HRF Amplitude
IQ, Height, Weight



Of course, you would need more then two subjects ...

Linear Model



System of Linear Equations

$$y1 = 1*b + x1*m$$
$$y2 = 1*b + x2*m$$

Matrix Formulation

$$\begin{bmatrix} y1 \\ y2 \end{bmatrix} = \begin{bmatrix} 1 & x1 \\ 1 & x2 \end{bmatrix} * \begin{bmatrix} b \\ m \end{bmatrix}$$

X = Design Matrix
b = Regression Coefficients
= Parameter estimates
= "betas"
= beta.mgh (mri_glmfit output)

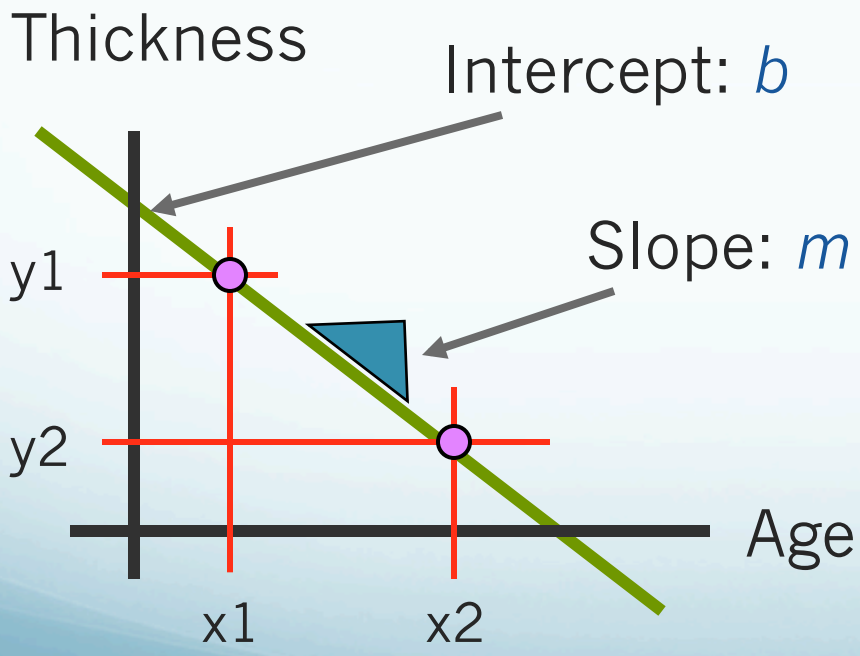
$$\mathbf{Y = X*b} \qquad \mathbf{b} = \begin{bmatrix} b \\ m \end{bmatrix}$$

Hypotheses and Contrasts

Is Thickness correlated with Age?
Does m = 0?
Null Hypothesis: H0: m=0

$$\begin{bmatrix} y1 \\ y2 \end{bmatrix} = \begin{bmatrix} 1 & x1 \\ 1 & x2 \end{bmatrix} * \begin{bmatrix} b \\ m \end{bmatrix}$$

$$m = [0\ 1] * \begin{bmatrix} b \\ m \end{bmatrix}$$



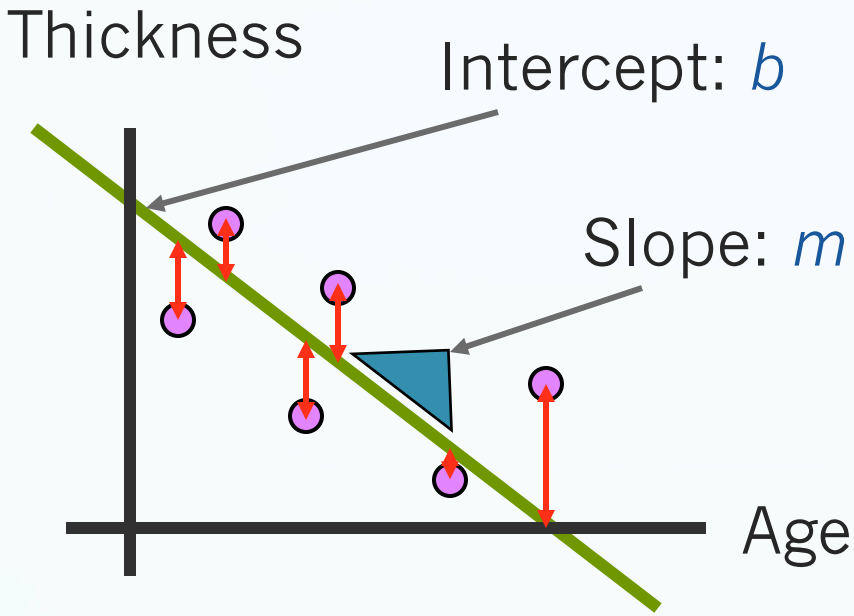
$$\mathbf{b} = \begin{bmatrix} b \\ m \end{bmatrix}$$

$$g = \mathbf{C}*\mathbf{b} \stackrel{?}{=} 0$$

C=[0 1]: Contrast Matrix

mri_glmfit output: gamma.mgh

More than Two Data Points



$$\begin{bmatrix} y1 \\ y2 \\ y3 \\ y4 \end{bmatrix} = \begin{bmatrix} 1 & x1 \\ 1 & x2 \\ 1 & x3 \\ 1 & x4 \end{bmatrix} * \begin{bmatrix} b \\ m \end{bmatrix} + \begin{bmatrix} n1 \\ n2 \\ n3 \\ n4 \end{bmatrix}$$

$$\mathbf{Y} = \mathbf{X}*\mathbf{b}+\mathbf{n}$$

$y1 = 1*b + x1*m + n1$
$y2 = 1*b + x2*m + n2$
$y3 = 1*b + x3*m + n3$
$y4 = 1*b + x4*m + n4$

- Model Error
- Noise
- Residuals
- eres.mgh

t-Test and p-values

$$\mathbf{Y = X*b+n}$$

$$g = \mathbf{C*b}$$

$$t = \frac{C * \beta}{\sqrt{\sigma^2 C * (X^T X)^{-1} C^T}}$$

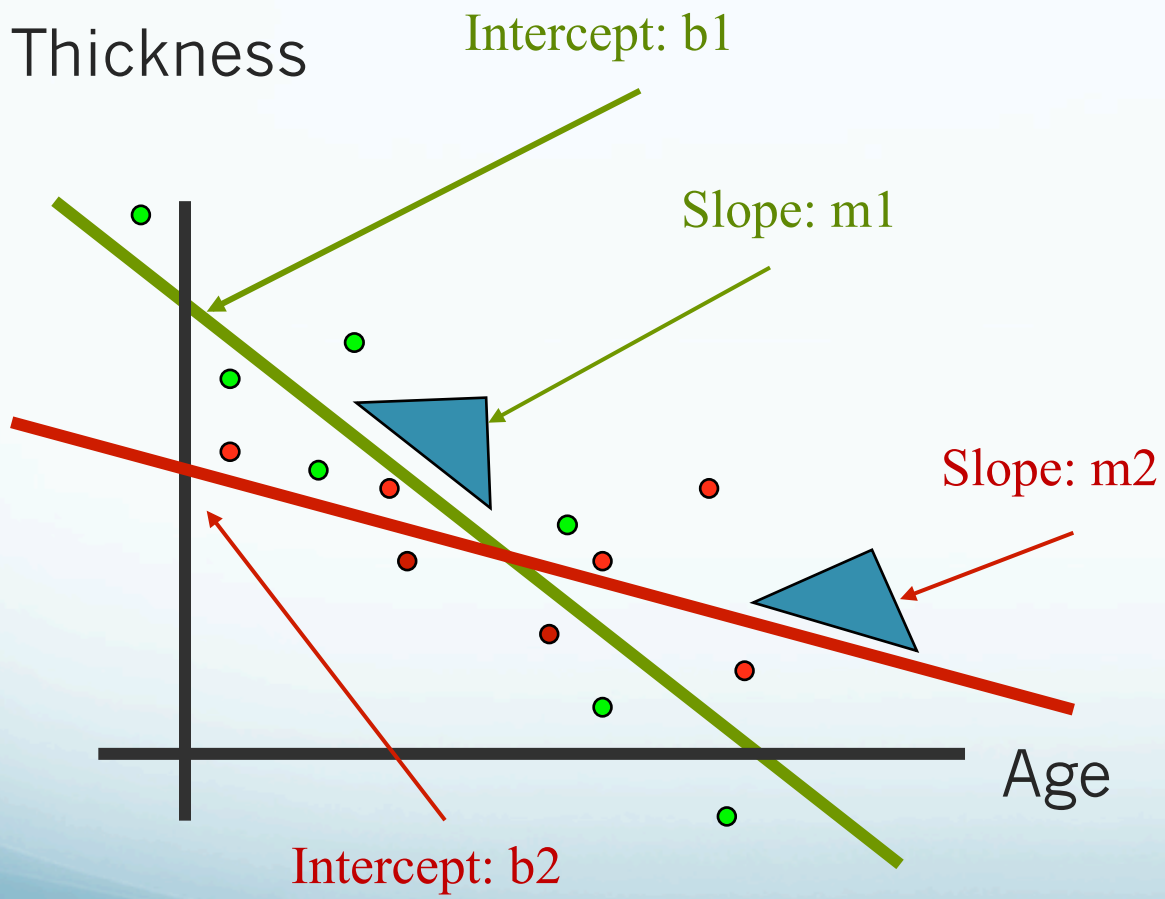
p-value/significance

- value between 0 and 1
- closer to 0 means more significant

FreeSurfer stores p-values as –log10(p):

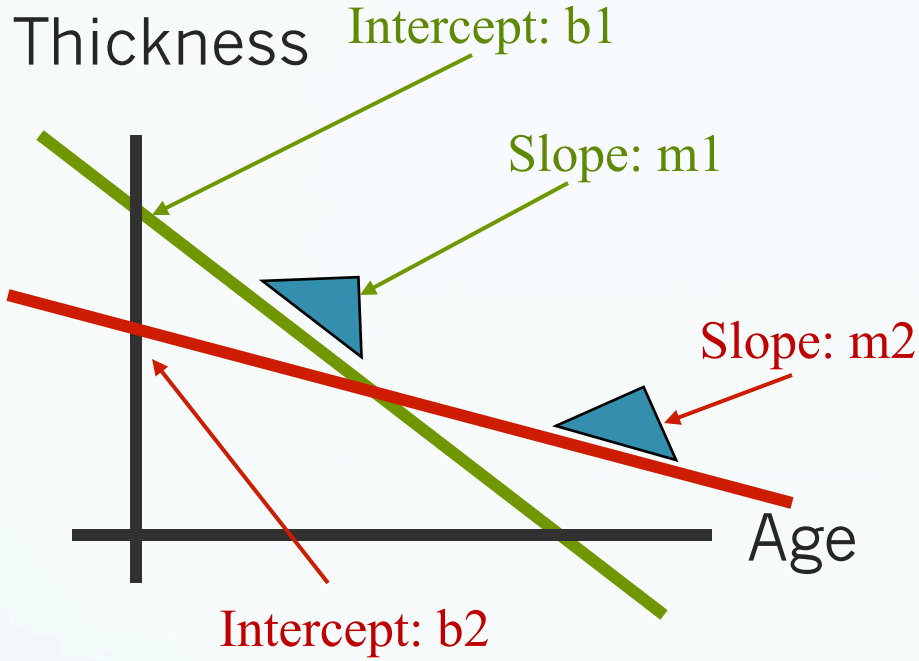
- $0.1=10^{-1}$→sig=1, $0.01=10^{-2}$→sig=2
- sig.mgh files
- Signed by sign of g
- p-value is for an unsigned test

Two Groups



- Do groups differ in Intercept?
- Do groups differ in Slope?
- Is average slope different from 0?
- …

Two Groups



$$\begin{bmatrix} y11 \\ y12 \\ y21 \\ y22 \end{bmatrix} = \begin{bmatrix} 1 & 0 & x11 & 0 \\ 1 & 0 & x12 & 0 \\ 0 & 1 & 0 & x21 \\ 0 & 1 & 0 & x22 \end{bmatrix} * \begin{bmatrix} b1 \\ b2 \\ m1 \\ m2 \end{bmatrix} + \mathbf{n}$$

$$\mathbf{Y = X*b+n}$$

$$y11 = 1*b1 + 0*b2 + x11*m1 + 0*m2 + n11$$
$$y12 = 1*b1 + 0*b2 + x12*m1 + 0*m2 + n12$$
$$y21 = 0*b1 + 1*b2 + 0*m1 + x21*m2 + n21$$
$$y22 = 0*b1 + 1*b2 + 0*m1 + x22*m2 + n22$$

Two Groups

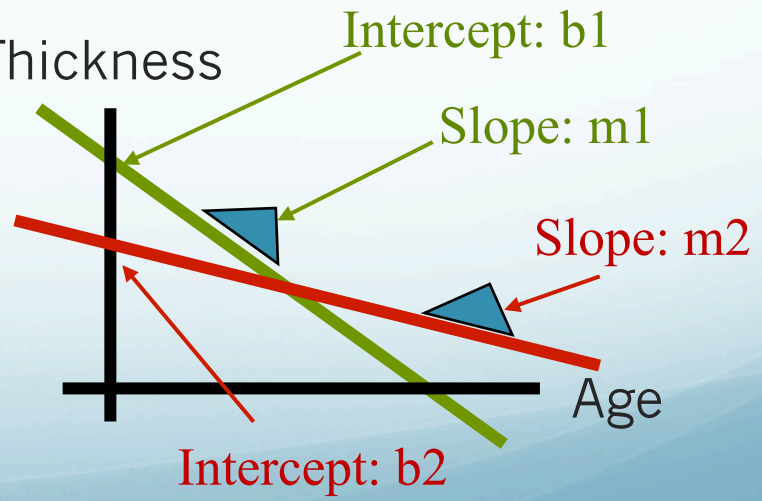
Do groups differ in Intercept?
Does b1=b2?
Does b1-b2 = 0?
C = [+1 -1 0 0], g = **C***b

Do groups differ in Slope?
Does m1=m2?
Does m1-m2=0?
C = [0 0 +1 -1], g = **C***b

Is average slope different than 0?
Does (m1+m2)/2 = 0?
C = [0 0 0.5 0.5], g = **C***b

$$\mathbf{Y = X*b+n}$$

$$\mathbf{b}= \begin{bmatrix} b1 \\ b2 \\ m1 \\ m2 \end{bmatrix}$$

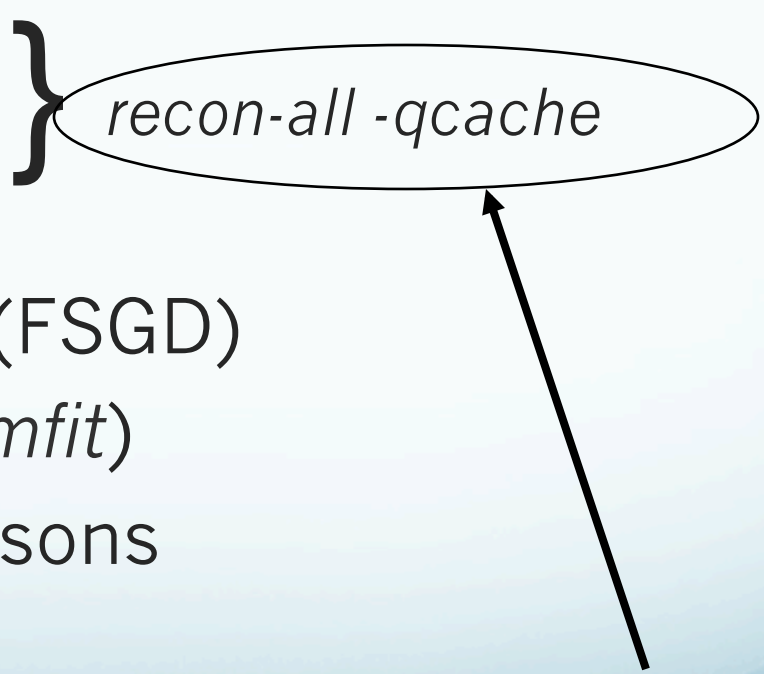


Surface-based Group Analysis in FreeSurfer

- Create your own design and contrast matrices
- Create an FSGD File
  - FreeSurfer creates design matrix
  - You still have to specify contrasts
- QDEC
  - Limited to 2 discrete variables, 2 levels max
  - Limited to 2 continuous variables

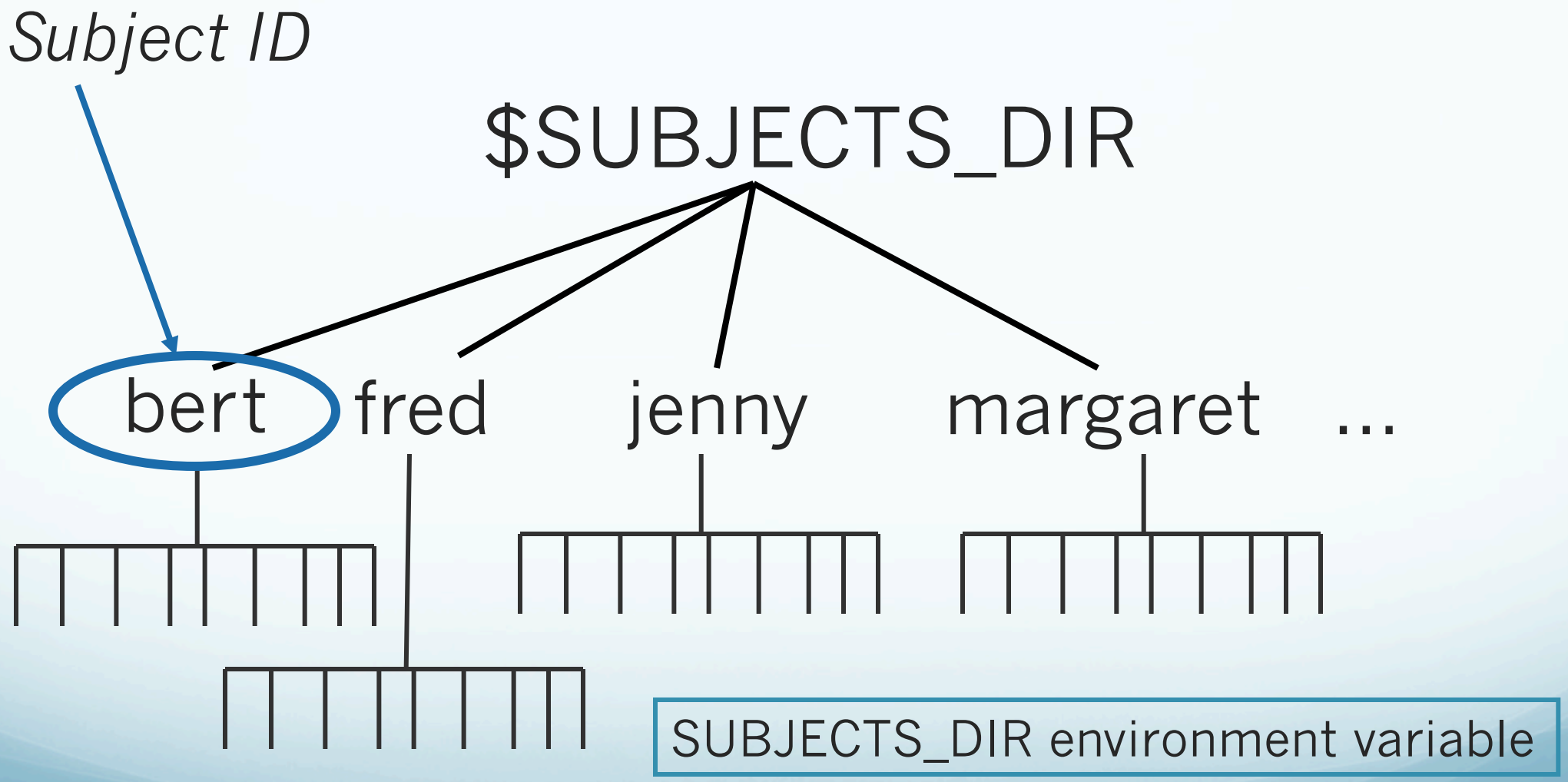
Command-line Processing Stages

- Assemble Data (*mris_preproc*)
  - Resample into Common Space
  - Smooth
  - Concatenate into one file
- Model and Contrasts (GLM) (FSGD)
- Fit Model (Estimate) (*mri_glmfit*)
- Correct for multiple comparisons
- Visualize (*tksurfer*)

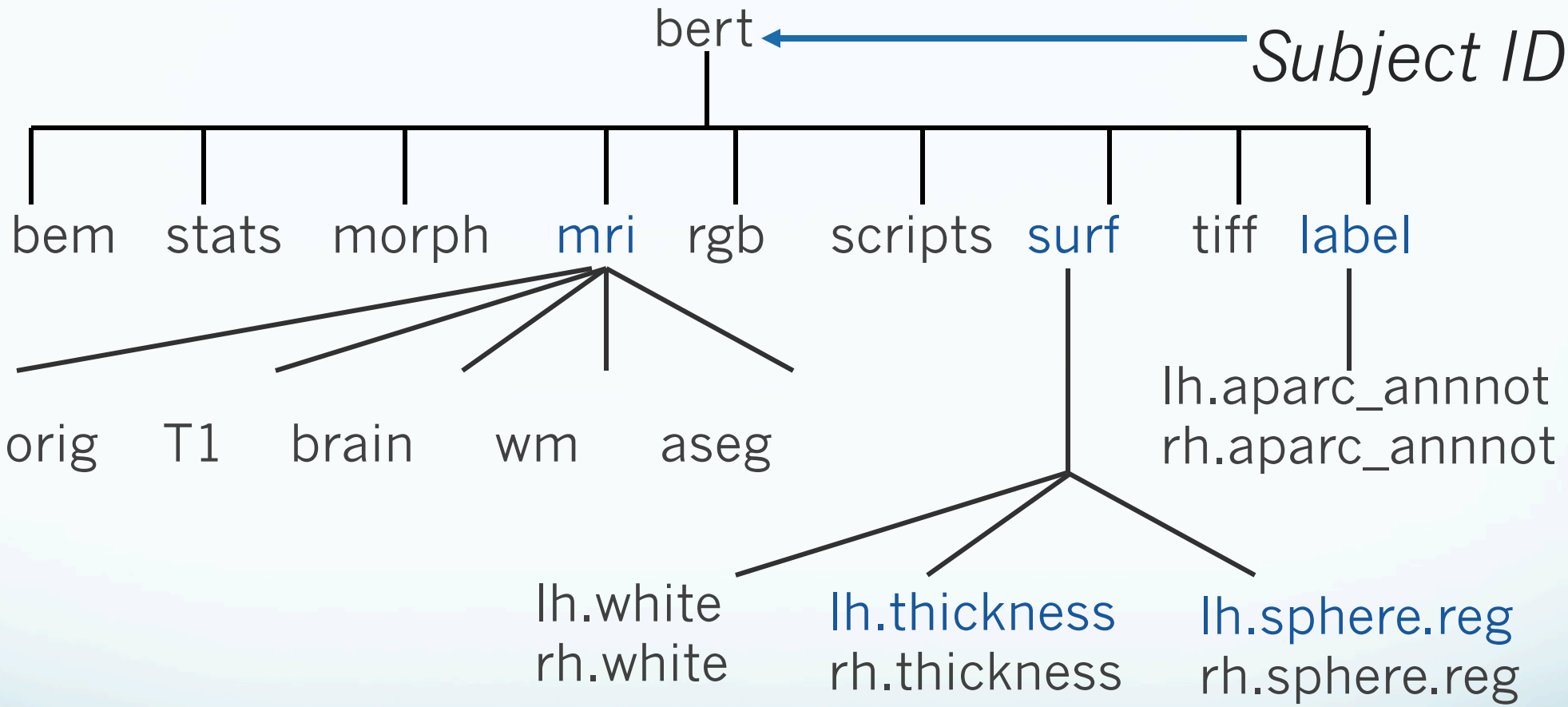


Run after all editing is done.

Specifying Subjects



FreeSurfer Directory Tree



SUBJECTS_DIR environment variable

Example: Thickness Study

1. $SUBJECTS_DIR/bert/surf/lh.thickness
2. $SUBJECTS_DIR/fred/surf/lh.thickness
3. $SUBJECTS_DIR/jenny/surf/lh.thickness
4. $SUBJECTS_DIR/margaret/surf/lh.thickness
5. …

FreeSurfer Group Descriptor (FSGD) File

- Simple text file
- List of all subjects in the study
- Accompanying demographics
- Automatic design matrix creation
- You must still specify the contrast matrices
- Integrated with tksurfer

Note: *Can* specify design matrix explicitly with --design

FSGD Format

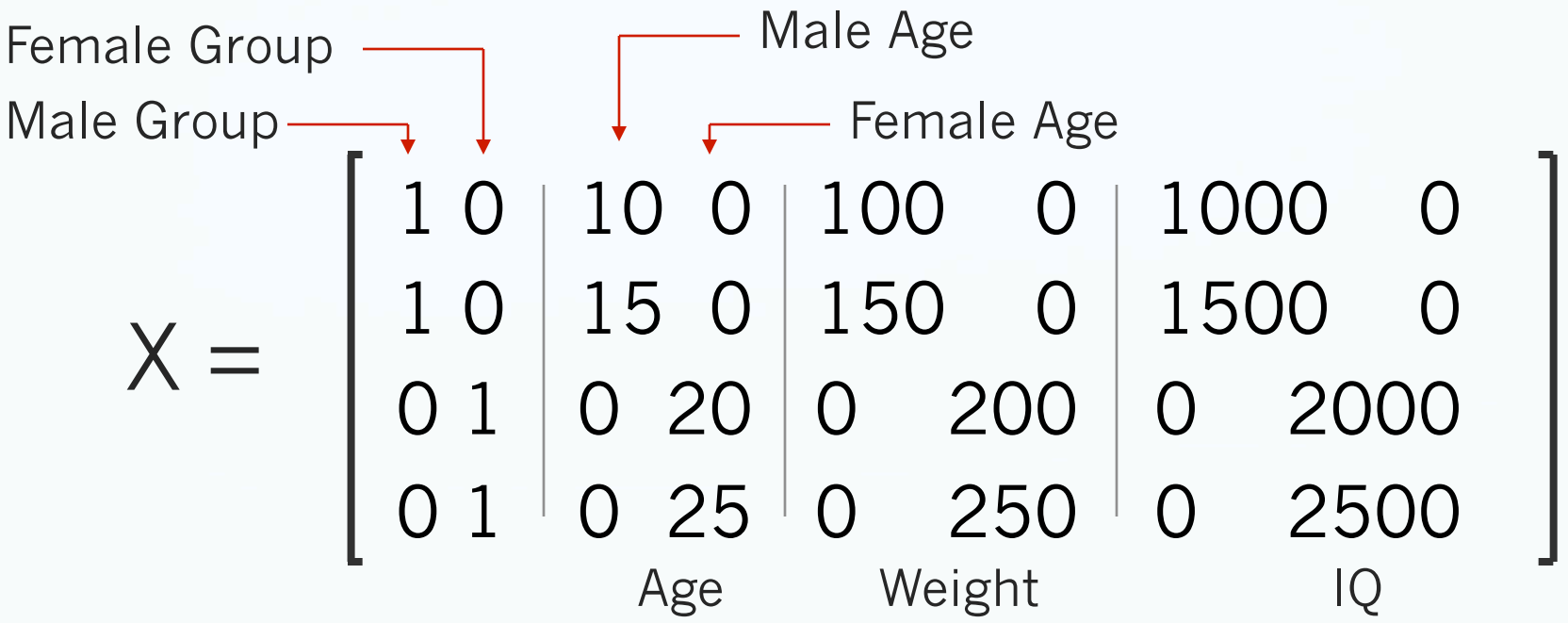
```
GroupDescriptorFile 1
Class Male
Class Female
Variables                          Age   Weight   IQ
Input bert       Male              10    100      1000
Input fred       Male              15    150      1500
Input jenny      Female            20    200      2000
Input margaret   Female            25    250      2500
```

- One Discrete Factor (Gender) with Two Levels (M&F)
- Three Continuous Variables: Age, Weight, IQ

Class = Group

Note: Can *specify* design matrix explicitly with --design

FSGDF → X (Automatic)



C = [-1 1 0 0 0 0 0 0]

Tests for the difference in intercept/offset between groups

C = [0 0 -1 1 0 0 0 0]

Tests for the difference in age slope between groups

Another FSGD Example

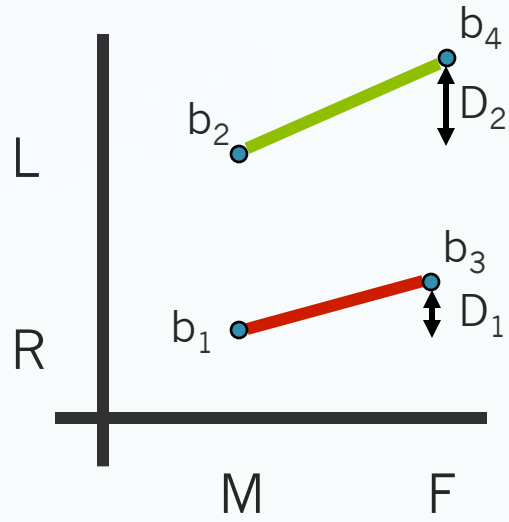
- Two Discrete Factors
  - Gender: Two Levels (M&F)
  - Handedness: Two Levels (L&R)
- One Continuous Variable: Age

```
GroupDescriptorFile 1
Class MaleRight
Class MaleLeft
Class FemaleRight
Class FemaleLeft
Variables                                   Age
Input bert              MaleLeft            10
Input fred              MaleRight           15
Input jenny             FemaleRight         20
Input margaret          FemaleLeft          25
```

Class = Group

Interaction Contrast

- Two Discrete Factors (no continuous, for now)
  - Gender: Two Levels (M&F)
  - Handedness: Two Levels (L&R)
- Four Regressors (Offsets)
  - MR (b_1), ML (b_2), FR (b_3), FL (b_4)




```
GroupDescriptorFile 1
Class MaleRight
Class MaleLeft
Class FemaleRight
Class FemaleLeft
Input bert          MaleLeft
Input fred          MaleRight
Input jenny         FemaleRight
Input margaret      FemaleLeft
```

$$g = D_1 - D_2 \overset{?}{=} 0$$

$$g = (b_3 - b_1) - (b_4 - b_2)$$

$$= -b_1 + b_2 + b_3 - b_4$$

$$C = [-1 \ +1 \ +1 \ -1]$$

Factors, Levels, Groups

Usually each Group/Class:

- Has its own Intercept
- Has its own Slope (for each continuous variable)
- NRegressors = NClasses * (NVariables+1)

Factors, Levels, Groups, Classes

Continuous Variables/Factors: Age, IQ, Volume, etc.

Discrete Variables/Factors:

Gender, Handedness, Diagnosis

Levels of Discrete Variables:

- Handedness: *Left and Right*
- Gender: *Male and Female*
- Diagnosis: *Normal, MCI, AD*

Group or Class: Specification of All Discrete Factors

- Left-handed Male MCI
- Right-handed Female Normal

Assemble Data: mris_preproc

mris_preproc --help

--fsgd FSGDFile : Specify subjects thru FSGD File
--hemi lh : Process left hemisphere
--meas thickness : subjectid/surf/hemi.thickness
--target fsaverage : common space is subject fsaverage
--o lh.thickness.mgh : output “volume-encoded surface file”

Lots of other options!

→ Output: lh.thickness.mgh – file with stacked thickness maps for all subjects
→ Input to Smoother or GLM

Surface Smoothing

- mri_surf2surf --help
- Loads stacked lh.thickness.mgh
- 2D surface-based smoothing
- Specify FWHM (eg, fwhm = 10 mm)
- Saves stacked lh.thickness.sm10.mgh
- Can be slow (~10-60min)
- recon-all –qcache (computes for each subject, run after you are finished editing subject)

mri_glmfit

- Reads in FSGD File and constructs **X**
- Reads in your contrasts (**C**1, **C**2, etc.)
- Loads data (lh.thickness.sm10.mgh)
- Fits GLM (ie, computes **b**)
- Computes contrasts (g=**C***b**)
- t or F ratios, significances
- Significance -log10(p) (.01 → 2, .001 → 3)

mri_glmfit

```
mri_glmfit
 --y lh.thickness.sm10.mgh
 --fsgd gender_age.txt
 --C age.mtx –C gender.mtx
 --surf fsaverage lh
 --cortex
 --glmdir lh.gender_age.glmdir
```

mri_glmfit --help

mri_glmfit

```
mri_glmfit
--y lh.thickness.sm10.mgh
--fsgd gender_age.txt
--C age.mtx –C gender.mtx
--surf fsaverage lh
--cortex
--glmdir lh.gender_age.glmdir
```

- Input file (output from smoothing).
- Stack of subjects, one frame per subject.

mri_glmfit

```
mri_glmfit
 --y lh.thickness.sm10.mgh
 --fsgd gender_age.txt
 --C age.mtx –C gender.mtx
 --surf fsaverage lh
 --cortex
 --glmdir lh.gender_age.glmdir
```

- FreeSurfer Group Descriptor File (FSGD)
- Group membership
- Covariates

mri_glmfit

```
mri_glmfit
 --y lh.thickness.sm10.mgh
 --fsgd gender_age.txt
 --C age.mtx –C gender.mtx
 --surf fsaverage lh
 --cortex
 --glmdir lh.gender_age.glmdir
```

- Contrast Matrices
- Simple text/ASCII files
- Test hypotheses

mri_glmfit

```
mri_glmfit
 --y lh.thickness.sm10.mgh
 --fsgd gender_age.txt
 --C age.mtx –C gender.mtx
 --surf fsaverage lh
 --cortex
 --glmdir lh.gender_age.glmdir
```

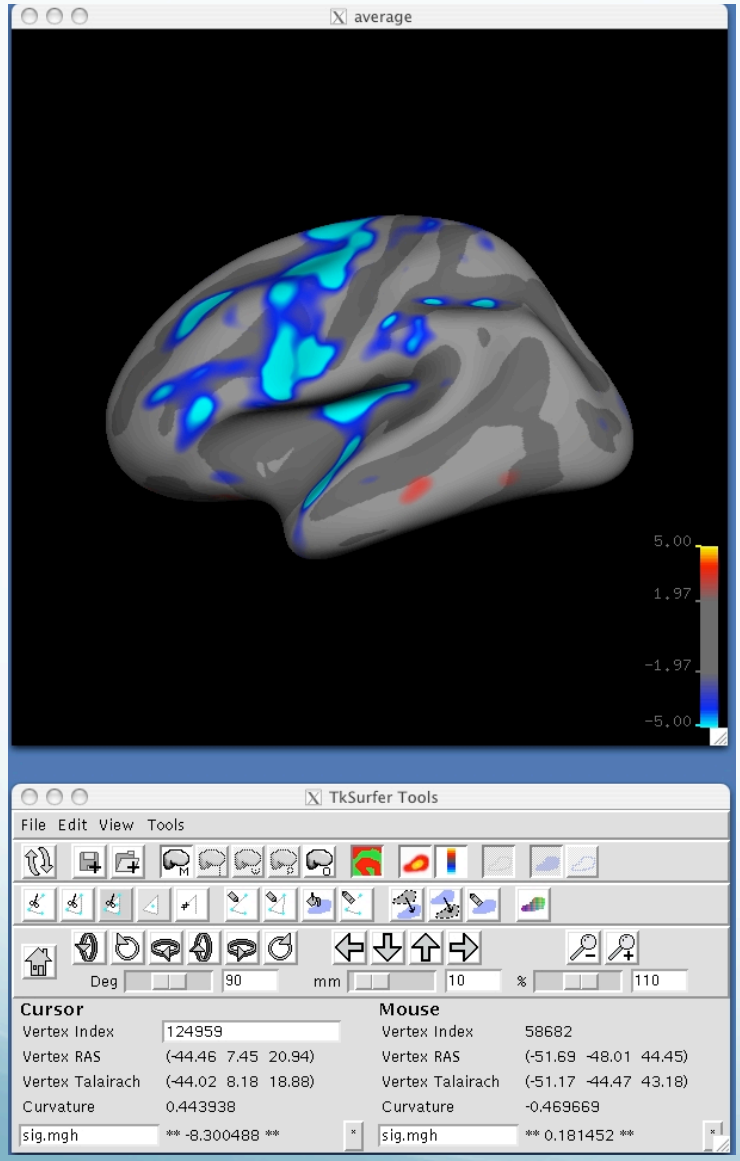
- Perform analysis on left hemisphere of fsaverage subject
- Masks by fsaverage cortex.label
- Computes FWHM in 2D

mri_glmfit

```
mri_glmfit
 --y lh.thickness.sm10.mgh
 --fsgd gender_age.txt
 --C age.mtx –C gender.mtx
 --surf fsaverage lh
 --cortex
 --glmdir lh.gender_age.glmdir
```

Output directory:
lh.gender_age.glmdir/
- beta.mgh – parameter estimates
- rvar.mgh – residual error variance
- etc …
- age/
  - sig.mgh – -log10(p), uncorrected
  - gamma.mgh, F.mgh
- gender/
  - sig.mgh – -log10(p), uncorrected
  - gamma.mgh, F.mgh

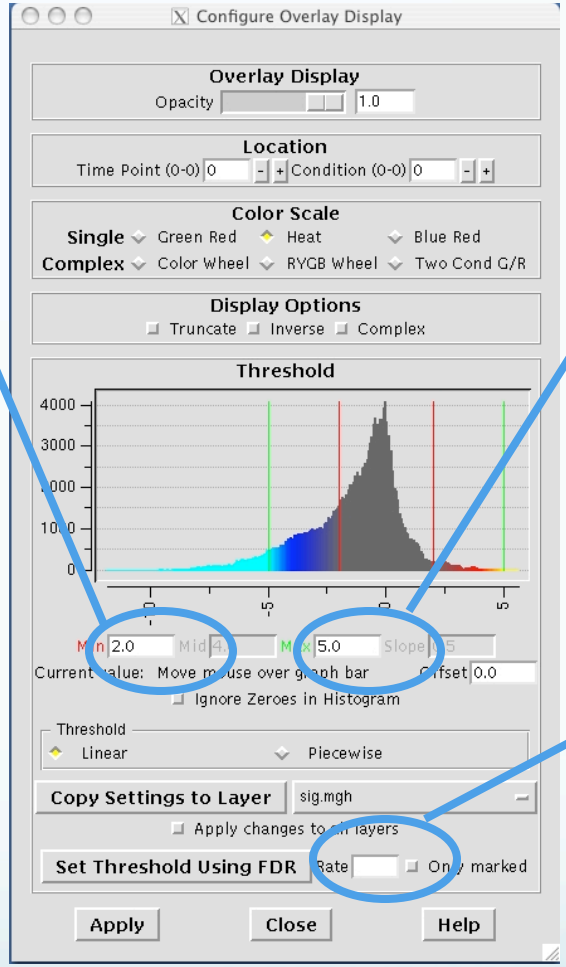
Visualization with tksurfer



File->LoadOverlay

Threshold:
-log10(p),
Eg, 2=.01

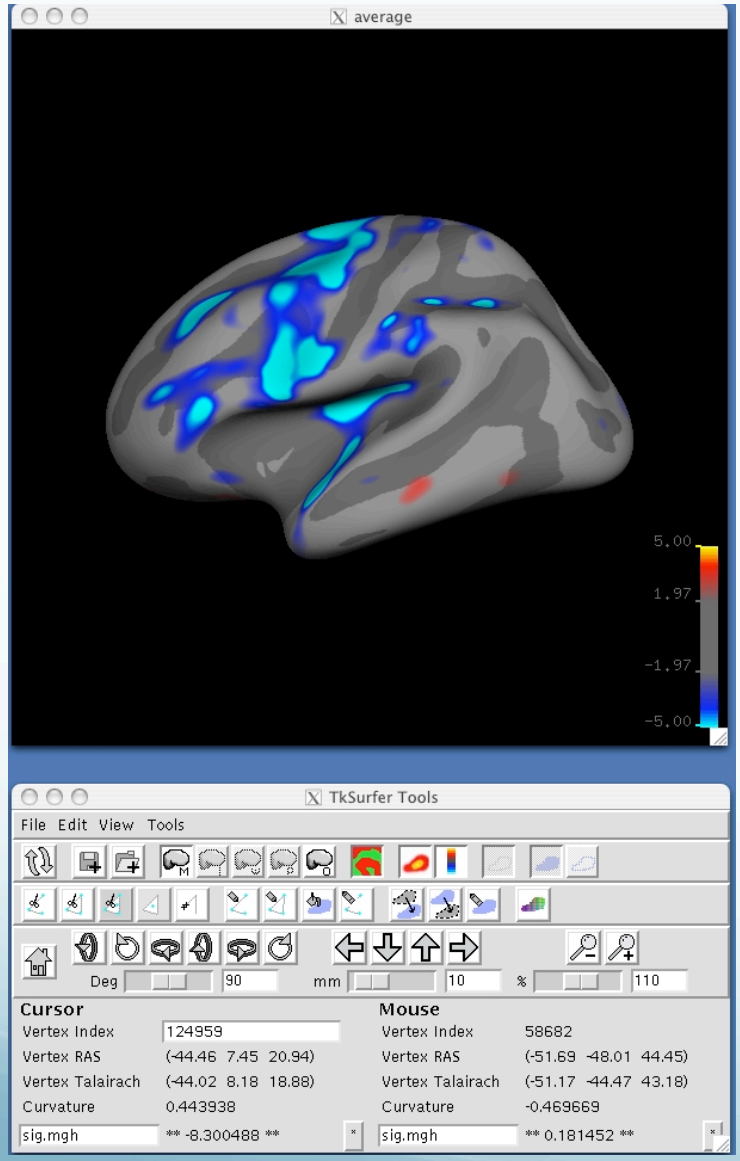
Saturation:
-log10(p),
Eg, 5=.00001

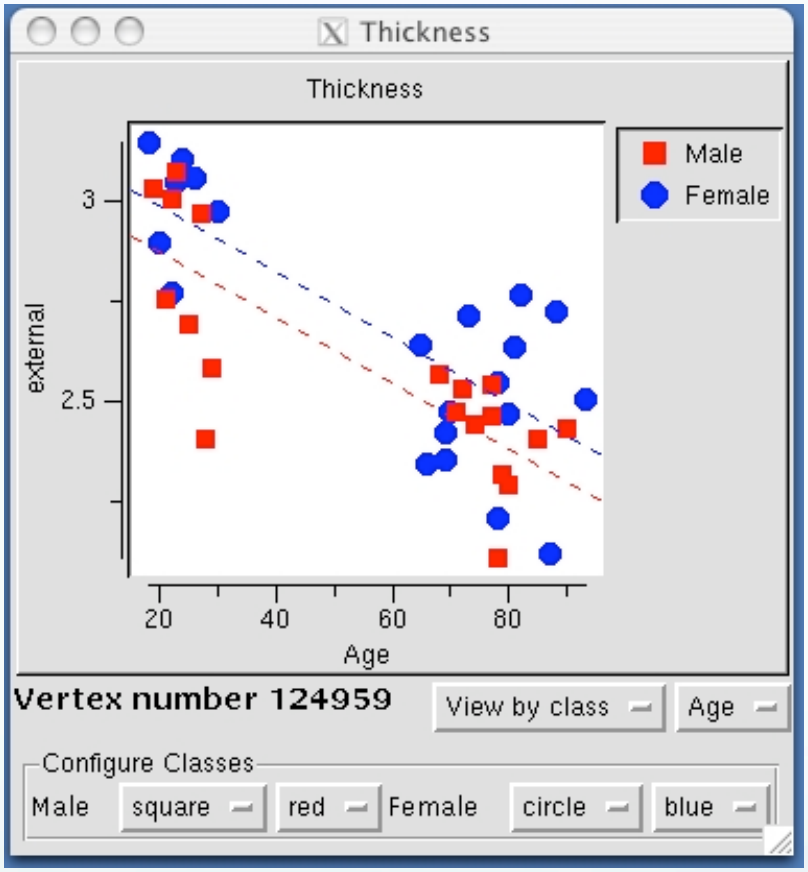


View->Configure->Overlay

False
Dicovery
Rate
Eg, .01

Visualization with tksurfer





File->
Load Group Descriptor File ...

Tutorial

Command-line Stream

- Create an FSGD File for a thickness study
- Age and Gender
- Run
  - mris_preproc
  - mri_surf2surf
  - mri_glmfit